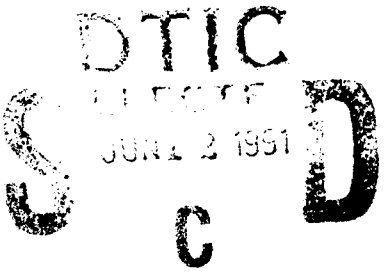

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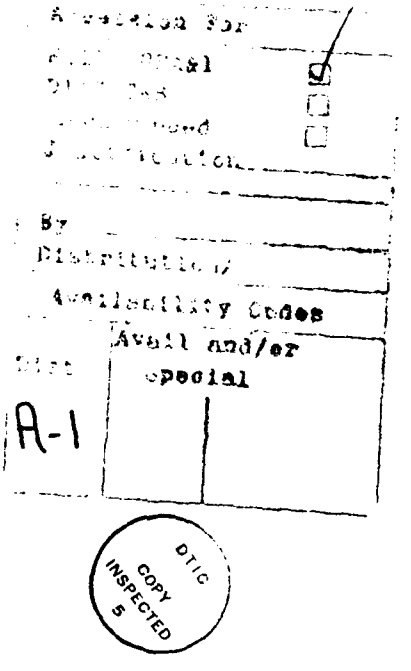
Numerical Solutions for Bayes Sequential Decision Approach to Bioequivalence Problem

Jing-Shiang Hwang
Department of Statistics
Harvard University



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Numerical Solutions for Bayes Sequential Decision Approach to Bioequivalence Problem

Jing-Shiang Hwang

Department of Statistics
Harvard University

March 20, 1991

Abstract

Bioequivalence is an important area of pharmaceutical research containing many questions which are not yet resolved. Various statistical approaches have been discussed in the literatures. We address stopping rules for testing bioequivalence from a decision-theoretic point of view. The numerical techniques for Bayes sequential decision problem are employed to obtain explicit descriptions of the solutions of the continuous time optimal stopping problem on bioequivalence.

Key words: Bioequivalence; Backward induction;Bayes risk; Decision theory; Optimal stopping; Sequential analysis; Wiener process.

1 Introduction

Two or more formulations of a drug are often compared in a bioequivalence trial. The purpose of such a trial is to determine whether alternative formulations which contain equal amounts of the same active ingredient give rise to comparable blood levels or produce, in some sense, equivalent therapeutic effects.

Usually several characteristics of the blood level concentration-time curves are considered. If a single dose of the drug is admistered, then the area under the curve (AUC), maximum concentration (CMAX) and the time at which the maximum concentration occurs (TMAX) all give useful information about the the extent and rate of absorption of the active ingredient of the formulations. The distributions of these values are usually not far from normal. For more discussion of the interpretation of relevant characteristics and design considerations associated with bioequivalence trials see Metzler (1974). A lot of authors have pointed out that a test of the usual null hypothesis is inappropriate since small and clinically insignificant differences may be detected with a large sample . Furthermore, as is always carefully underlined in introductory statistics courses, failure to reject the null hypothesis does not imply its affirmation. Considerable controversy has arisen over the appropriateness of different approaches. For such discussions, the reader is directed to the articles by O'Quigley and Baudoin (1988) for general approaches and Selwyn *et al.* (1981) for the use of the Bayesian approach.

We address stopping rules for testing bioequivalence from a Bayes sequential decision-theoretic point of view. Bather and Chernoff (1988) have derived a formulation where sums of successive observations of differences are replaced by a continuous time Wiener process. Using several fundamental advantages of the continuous time problem over the discrete time problem for which it is an approximation, they also obtained rough bounds and asymptotic approximations for the solution of the continuous time problem. While these bounds and asymptotic approximations provide valuable insight, they do not provide an adequate approximation to the solution.

In this paper we will employ simple numerical techniques which are described in detail by Chernoff and Petkau (1986) to obtain explicit descriptions of the solutions of this continuous time problem. The basic idea is straightforward: the Wiener process is approximated by a discrete time process and backward induction is employed to solve the optimal stopping problem for

this new process. Then this solution, properly adjusted, can be used to approximate that of the continuous time problem. This approximation can then itself be adjusted further to approximate the solution of the original discrete time bioequivalence problem.

2 Statement of the Problem

We consider a trial with a parallel design for comparing two formulations, a new formulation and the standard. The design allows a drug experimenter to terminate the program early if the two formulations are almost equivalent or far from equivalent and to continue the trial otherwise . Before looking at the sequential approach we recall the main ideas. Let μ, measured on some scale, represent the true difference between the two population treatment means. In the process we will estimate μ. As pointed out we will be unable to infer $\mu = 0$, and even were we able to infer $\mu \neq 0$ this may be of little practical assistance if μ seems to be close to zero.

The Bayesian approach allows, in fact requires, explicit consideration of the information available concerning the drug separate from the current trial. For example, the drug manager may be quite sure, on the basis of previous studies, that the difference of the two formulations is very small. On the other hand, despite these other studies, the bioequivalence of these drugs may still be in doubt, in part perhaps because previous experience has focused on a rather narrow patient population. This information should be used explicitly in deciding the course of the drug's clinical program.

Consistent with the Bayesian approach, the prior information is quantified in terms of a (prior) probability distribution on μ. To be specific we assume

$$\mu \sim N(\mu_0,\ \sigma_0^2).$$

If μ_0 and σ_0 are close to zero then the manager's prior assessment is that the two formulations are likely to be bioequivalent; and large σ_0 corresponds to a high degree of uncertainty regarding μ. The roles of μ_0 and σ_0 will be made clear in the following development.

Let X_i denote the difference responses for i-th pair of patients, $i = 1, \ldots, n$. Assume the sequential random sample $X_1, \ldots, X_n$ are independent $\mathrm{N}(\mu, \sigma^2)$, where σ^2 is known (the unknown variance case is more realistic but is not conceptually different).

The posterior distribution of μ given $X_1, \ldots, X_n$ is

$$\mathcal{L}(\mu|X_1, \ldots, X_n) = N(Y_n, s_n),$$

where

$$Y_n = \frac{\mu_0\sigma_0^{-2} + (X_1 + \cdots + X_n)\sigma^{-2}}{\sigma_0^{-2} + n\sigma^{-2}} \tag{1}$$

and the precision

$$s_n^{-1} = \sigma_0^{-2} + n\sigma^{-2}$$

increases linearly in n.

So after each observation, we need to know n, the current Bayes estimate Y_n of μ, and its precision s_n ; (Y_n, s_n) is the "state of information" after the n-th observation. Then we may decide to continue sampling or to stop. In the latter case we must decide on whether or not we have bioequivalence. While it will be only approximately true in practice, we assume that the cost of the trial is linear in the number of pairs of patients in the experiment. That is we assume that the marginal sampling cost per pair is c. When the trial is stopped, one must decide to reject or claim bioequivalence. The cost of rejecting bioequivalence is k, the expected cost of having to start over. In the following discussion we first consider the case where the cost of claiming bioequivalence is μ^2.

Now let us compute the posterior risk of stopping at stage n. We have the risk associated with stopping and deciding for or against bioequivalence plus the cost of sampling cn yielding $d(Y_n,\ s_n)$, where

$$\begin{aligned} d(y,s) &= cn + \min\{k,\ E[\mu^2|Y_n = y, s_n = s]\} \\ &= cn + \min\{k,\ y^2 + s\} \\ &= \frac{c\sigma^2}{s} + \min\{k,\ y^2 + s\} - \frac{c\sigma^2}{\sigma_0^2}. \end{aligned} \tag{2}$$

The problem of finding the Bayes procedure for the bioequivalence problem has been reduced to a standard stopping problem of the type described in Chernoff (1972).

Stopping Problem : Let $(Y_n,\ s_n,\ n \in G)$ be a Gaussian process of independent increments starting from $(Y_{n_0}, s_{n_0}), n_0 \in G$, with

$$\mathcal{L}(Y_n - Y_m|Y_m) = N(0, s_m - s_n),\ n \geq m, \tag{3}$$

and let the cost associated with stopping at (Y_n, s_n) be given by $d(Y_n, s_n)$. Find a stopping rule (a random variable N taking on values in G such that $\{N = n\} \in \mathcal{B}\{Y_i : i \in G, n_0 \leq i \leq n\}$) so as to minimize

$$E[d(Y_N, s_N)]. \tag{4}$$

3 Continuous time stopping problem

The continuous time stopping problem has a number of fundamental advantages over the discrete time problem for which it is an approximation. First, the continuous time problem can be normalized so that many of the parameters which appear in the original (discrete time) problem are eliminated; thus a single continuous time problem corresponds to an entire class of discrete time problem. Second, the continuous time problem for a Wiener process where the cost associated with stopping depends only on the stopping point is related to a problem in analysis, a free boundary problem involving the heat equation. This relationship facilitates obtaining bounds and asymptotic approximations for the solution of the continuous time problem.

For the bioequivalence problem, μ is regarded as a random variable, and the limiting form of the (Y_n, s_n) process is a Gaussian process of independent increments $Y(s)$ in the $-s$ scale for $s_0 \geq s \geq s^0$, where

$$E[dY(s)] = 0, \quad Var[dY(s)] = -ds,$$

with $Y(s_0) = \mu_0$ at $s_0 = \sigma_0^2$ and

$$s^{-1} = \sigma_0^{-2} + t\sigma^{-2}.$$

Note that as time t increases from 0 to ∞, s decreases from σ_0^2 to 0. Thus $(-ds)$ may be thought of as positive. Hence a limiting form of the bioequivalence problem is a special case, for $G = (0, \infty)$, of the following continuous time stopping problem.

Stopping problem : Given a Gaussian process $\{Y(s), s \in G\}$ of independent increments in the -s scale, with $EdY(s) = 0$, $Var[dY(s)] = -ds$, starting at $Y(s_0) = y_0$, find a stopping time S (S is a random variable on G, where $\{ S = s \} \in \mathcal{B} \{Y(s') : s_0 \geq s' \geq s\}$) to minimize the *risk*

$$E[d(Y(S), S)].$$

The continuous time version of the bioequivalence problem is essentially associated with the cost function

$$d(y,s) = \frac{c\sigma^2}{s} + \min\{k, y^2 + s\},$$

after dropping the constant $c\sigma^2/\sigma_0^2$ which does not affect the choice of the optimal procedure.

Not only is the continuous time problem a limiting form of the discrete time problem, but we may regard the latter as *embedded* in the continuous time problem subject to the restriction that stopping may take place only at certain specified values of s, i.e., $s = (\sigma_0^{-2} + t\sigma^{-2})^{-1}$ for integer values of t. In this continuous time framework, Y is regarded as a function of s and the subscript n has been eliminated as an unnecessary parameter which serves only to mark the possible stopping times.

From the point of view of solving the bioequivalence problem, certain simplifying transformations can be made. The transformation

$$\begin{aligned} Y^*(s^*) &= aY(s) \\ s^* &= a^2 s \end{aligned}$$

converts the $Y(s)$ to the $Y^*(s^*)$ process which is also a Gaussian process of independent increments with $E[dY^*(s^*)] = 0$, and

$$Var[dY^*(s^*)] = a^2 Var[dY(s)] = -a^2 ds = -ds^*.$$

Then taking $a = k^{-1/2}$, we have

$$\begin{aligned} d^*(y^*, s^*) &= k^{-1}\,(d(y,s) - k) \\ &= k^{-1} c\sigma^2 a^2 s^{*-1} + \min\{0, k^{-1}a^{-2}(y^{*2} + s^*) - 1\} \\ &= k^{-2} c\sigma^2 s^{*-1} + \min\{0, y^{*2} + s^* - 1\} \\ &= \frac{c^*}{s^*} + \min\{0, y^{*2} + s^* - 1\} \qquad (5) \end{aligned}$$

Thus our problem may be normalized by this transformation to that of dealing with stopping cost d^* with one sampling cost parameter $c^* = c\sigma^2 k^{-2}$. Now drop the stars, we have a standard form of optimal stopping problem with

$$d(y,s) = \frac{c}{s} + \min\{0, y^2 + s - 1\}. \qquad (6)$$

This form involves only the single parameter c.

4 Numerical techniques

Chernoff and Petkau (1986) have described a number of techniques to be employed in obtaining numerical descriptions of the solutions of the general optimal stopping problem for a zero drift Wiener process in the (y, s) scale. Using the same approach, we can create a slightly modified program to solve the bioequivalence program. In this section, we will review the general numerical techniques of Bayes sequential decision problems.

The solution of a continuous time optimal stopping problem can be expressed in terms of a *stopping set* $\mathcal{S}$ and a *continuation set* $\mathcal{C} = \mathcal{S}^c$ in the (y, s) plane; that is, S consists of stopping when $(Y(s), s)$ reaches $\mathcal{S}$ as s decreases from s_0. This is related to that of a corresponding free boundary problem involving the heat equation. More precisely, that free boundary problem is to find $(\mathcal{S},b)$ so that

$$\begin{aligned} \frac{1}{2} b_{yy}(y,s) &= b_s(y,s) \quad \text{for } (y,s) \in \mathcal{C}, \\ b(y,s) &= d(y,s) \quad \text{for } (y,s) \in \mathcal{S}, \\ b_y(y,s) &= d_y(y,s) \quad \text{for } (y,s) \in \partial\mathcal{S}, \end{aligned} \tag{7}$$

where $\partial\mathcal{S}$ is the boundary of $\mathcal{S}$. The solution b of the free boundary problem corresponds to the optimal risk $\hat{d}$ of the stopping problem, that is,

$$b(y_0, s_0) = \hat{d}(y_0, s_0) = E[d(Y(S), S)]. \tag{8}$$

As mentioned before, the discrete time version of the problem can be regarded as a special case of the continuous time version where stopping is restricted to a limited subset of the (y, s) space, and hence the optimal risks and related stopping sets are larger. In the discrete time problem, the intervals between successive values of s are not equal. For convenience in the numerical approximation to the solution of the continuous time problem, we introduce another discrete time problem where the successive values of s are equally spaced. Moreover, the discrete time solution converges monotonically to the continuous time solution if the set of possible stopping times $\{s^0 + i\,\delta, i = 0, 1, \ldots\}$ increases and $\delta \to 0$. While the value of s in the stopping times set decreases by δ between these succesive possible stopping times, the process $Y(s)$ changes by a normal deviate with mean 0 and variance δ; in effect, the Wiener process is being approximated by a

sum of independent normal random variables. At any point (y, s) where s corresponds to a permissible stopping time, the choice between either stopping at this point or continuing on to next permissible stopping time and proceeding optimally thereafter is made on the basis of which of $d(y, s)$ or $E[\hat{d}(Y(s-\delta), s-\delta)|Y(s) = y]$ is smaller. Thus, the backward induction algorithm which yields the optimal solution to the stopping problem for this discrete process is specified by

$$\begin{aligned} \hat{d}(y, s) &= d(y, s) \text{ for } s = s^0, \\ &= \min\{d(y, s), E[\hat{d}(y + Z\sqrt{\delta}, s - \delta)]\} \text{ for } s > s^0, \end{aligned} \tag{9}$$

where Z represents a standard normal deviate.

Note that the evaluation of the expectation appearing in (9) would require a numerical integration for which purpose the y-axis would have to be discretized also. Thus, in practice, the backward induction is carried out on a grid of (y, s) points, each of which is classified as either a stopping or a continuation point during the course of the computation. How would one use the results of the backward induction algorithm (9) to obtain approximations to the boundary $\tilde{y}(s)$ of the continuation region for the continuous time problem ? Chernoff (1965) presents a detailed investigation of the relation of the discrete time normal problem to the continuous time problem. His method consists of simply adjusting the boundary of the optimal continuation region for discrete time problem; that is the form

$$\tilde{y}_\delta(s) = \tilde{y}(s) \pm 0.5826\sqrt{\delta}, \tag{10}$$

where $\tilde{y}_\delta$ and $\tilde{y}$ represent the optimal boundaries for the discrete and continuous time versions and the sign is determined so as to make the continuation region for the continuous time version larger. This correction may be used to go from the backward induction to the continuous time version, and then again to go from the latter to the original discrete time problem.

To avoid the time consuming numerical integration, the standard normal deviate in (9) is replaced by a random variable which is $\pm$ 1, each with probability 1/2, leading to the algorithm

$$\begin{aligned} \hat{d}(y, s) &= d(y, s) \text{ for } s = s^0, \\ &= \min\{d(y, s), \frac{1}{2}[\hat{d}(y + \sqrt{\delta}, s - \delta) + \hat{d}(y - \sqrt{\delta}, s - \delta)]\} \text{for } s > s^0. \end{aligned} \tag{11}$$

We relate this algorithm to a discrete time binomial problem which is different from (9) which corresponds to a discrete time normal problem. For the discrete binomial approximation (11), the discretization of the y-axis is necessarily related to the discretization of the s-axis. Whereas the Wiener process was previously being approximated by the sum of its increments, in this simpler approximation the increment of the Wiener process is itself replaced by a Bernoulli random variable. While the second moment of the Bernoulli variable is chosen to match that of the increment it is replacing, the higher even moments do not match. Chernoff and Petkau (1986) have described another continuity correction for the solution of the discrete time version with Bernoulli increments. Defining

$$D(y,s) = \hat{d}(y,s) - d(y,s),$$

where $\hat{d}$ is the optimal risk in the discrete time problem (the function evaluated by the algorithm(11)) for $y(s) \in \mathcal{C}$ and close to the $\tilde{y}(s)$, the correction is to use the values D_0 and D_1 of D at $y_0^*(s)$ and $y_1^*(s)$, the continuation points on the grid which are closest and second closest to the stopping region at the stopping time s, and the continuity correction becomes

$$\tilde{y}(s) = y_0^*(s) \pm v\sqrt{\delta}, \tag{12}$$

where

$$v = \frac{D_1}{4D_0 - 2D_1}. \tag{13}$$

The sign is plus (minus) when $\mathcal{C}$ is above (below) $\mathcal{S}$. Thus, by applying two corrections we can approximate the solution to the original discrete time normal version of our optimal stopping problem. That is, we calculate the backward induction solution with the discrete time Bernoulli process, use (12) to approximate the solution to the continuous time problem and end by applying (10) to estimate the solution to the original discrete time normal version.

5 Implementation

For the bioequivalence problem, the symmetry of $d(y,s)$ about $y = 0$ implies that the computations involved in the backward induction can be confined

to $y \geq 0$, that is, computing on the grid

$$\{(y,s) : s = s^1 + i\,\delta,\ y = j\sqrt{\delta}; i = 0,1,\ldots,m_s, j = 0,1,\ldots,m_y\}. \qquad (14)$$

The computation proceeds in steps: At the initial step, the values of $\hat{d}$ are assigned at all points of the grid corresponding to the initial value s^1, say $s^1 = s^0 = 0$. We remark here that in contrast to the continuous time problem, the discrete time stopping problem under consideration, (which we shall call the random walk problem), has the property that the continuation region is truncated; that is, there exists an interval in the s-axis, $[0, r\delta]$, on which none of the grid points will be classified as continuation points. In fact for $s = \delta$, $\hat{d}(y,\delta) = d(y,\delta)$ because $d(y,0) = \infty$. Knowing $\hat{d}(y,i\delta)$ we can calculate $\hat{d}(y,(i+1)\delta)$, and it turns out that for several steps, there are no continuation points and $\hat{d}(y,i\delta) = d(y,i\delta)$ for $i = 1,2,\ldots,r$; Then for $i \geq r+1$, continuation points appear.

In the course of this computation which yields the optimal risk for the random walk problem, each of the individual grid points is classified as either a stopping point or a continuation point for the random walk. Thus, the continuation regions and their boundaries are determined and continuity correction methods can be employed to obtain approximations to the continuous time boundaries. For accuracy we start with a small step size δ. The use of a small grid spacing in a backward induction designed to obtain estimates for large values of s could require an exorbitant amount of computer time. On the other hand, while the use of a large grid spacing may allow the determination of reasonably good estimates at large values of s, the estimates obtained for small values of s would be poor. Thus the computation is carried out in stages or *phases* where grid spacings are changed from one phase to the next.

The first phase consists of starting at $s^1 = 0$ and applying m_s steps of size δ for a suitably small value of δ. Then m_y, the number of grid points along the y-axis, must be chosen large enough to contain all the continuation points for this first phase. In the next phase we increase the size of δ by a factor of 4 which automatically doubles the grid distance along the y-axis. Instead of starting phase 2 at the end of phase 1 where $s = m_s\delta$, we prefer to overlap these two phases, to give the new coarser calculation an opportunity to adjust, thereby avoiding some possible discontinuities due to the transition. Thus we have a new δ, four times the original, and a new s^1

between the original s^1 and $s^1 + m_s\delta$, and new values of m_s and m_y. Where we have overlapping phases, we use the finer grid to determine the values of the Bayes risk and optimal stopping boundaries to be used for publication. This procedure can be repeated in successive phases of coarsening the grid.

Referring to Figure 1, we see that there are two boundaries above the y-axis. For sufficiently large values of the constant c, the outer boundary turns back toward the s-axis. It is possibly desirable to change δ again so that the grid spacings become more refined as the boundary gets close to the s-axis. It is possible to refine the grids by *reducing* δ by a factor 4 when moving to the next phase. In this case the new s^1 will be the last value of s, i.e., $s^1 + m_s\delta = s^*$. Now we face a technical difficulty. If we label the old and new values of δ, δ_o and $\delta_n = \delta_o/4$, then the new values of y are $i\sqrt{\delta_n} = i\sqrt{\delta_o}/2$ and we can not proceed because we have not evaluated $\hat{d}$ at $i\sqrt{\delta_n} = i\sqrt{\delta_o}/2$ for the odd values of i when $s = s^*$.

To overcome this difficulty we evaluate $\hat{d}(y, s^*)$ for $y = i\sqrt{\delta_o}/2$ for odd values of i, by replacing the last dichotomous step of $\pm\sqrt{\delta_o}$ by a four valued step with the same mean 0 and variance δ_0. In other words if we let y go to

$$y \pm \frac{1}{2}\sqrt{\delta_o} \text{ with probability } p_1,$$

and

$$y \pm \frac{3}{2}\sqrt{\delta_o} \text{ with probability } p_2,$$

(where $y = i\sqrt{\delta_o}/2$ for odd i), then the mean change $E[dY] = 0$ and the variance $E[dY]^2 = \delta_o$ if

$$\begin{aligned} p_1 + p_2 &= \frac{1}{2} \\ p_1 + 9\,p_2 &= 2, \end{aligned}$$

i.e. $p_1 = 5/16$ and $p_2 = 3/16$. Thus for these intermediate values of y, the Bayes risk at (y, s^*) will be the minimum of $d(y, s^*)$ and

$$\begin{aligned} \hat{d}(y, s^*) &= \frac{5}{16}\hat{d}(y - \frac{1}{2}\sqrt{\delta_o}, s^* - \delta_o) + \frac{5}{16}\hat{d}(y + \frac{1}{2}\sqrt{\delta_o}, s^* - \delta_o) \\ &\quad + \frac{3}{16}\hat{d}(y - \frac{3}{2}\sqrt{\delta_o}, s^* - \delta_o) + \frac{3}{16}\hat{d}(y + \frac{3}{2}\sqrt{\delta_o}, s^* - \delta_o). \quad (15) \end{aligned}$$

Having calculated these values we can now proceed with the numerical calculations using the reduced value δ_n of δ. We expect this technique would reveal

slight discontinuities in the estimates of both the Bayes risk and the stopping boundary on moving from one phase to the next. But the experiment shows that the jumps are so small that we can ignore them.

6 Numerical Solutions

Bather and Chernoff (1988) have characterized the general picture of the solutions by studying the effect of changing the standardized sampling cost parameter c. First, the optimal continuation region $\mathcal{C}$ will cover the curve $y = \pm\sqrt{1-s}$ for $0 < s < 1$. This is because the discontinuity in first derivatives of the stopping cost $\min\{0, y^2 + s - 1\}$ implies a local advantage in sampling. The advantage is of order $\sqrt{|\delta s|}$, whereas the sampling cost is of order $|\delta s|$. Secondly $\mathcal{C}$ is monotone in the sampling cost c, that is, $c_1 \geq c_2$ implies $\mathcal{C}_1 \subset \mathcal{C}_2$. Third, every point on the parabala $y^2 + s - 1 = 0$ belongs to $\mathcal{C}$, with the possible exception of $(y, s) = (0,1)$. In fact, there is a definite advantage in sampling if $c < \sqrt{2/\pi e} \doteq 0.484$, *i.e.*, $(0,1) \in \mathcal{C}$ if $c < \sqrt{2/\pi e}$. Fourth, for $c \geq 1$, all points $(0, s)$ lie in the optimal stopping set $\mathcal{S}$ and for $0 < c \leq 1$, all points $(0, s)$ with $0 \leq s \leq \sqrt{c}$ also lie in $\mathcal{S}$. Furthermore,

$$(y, s) \in \mathcal{S} \quad \text{if } c > \frac{1}{4} \text{ and } s \geq \frac{c}{2\sqrt{c} - 1}.$$

From the above results, they have drawn the stopping boundaries roughly for $c \geq 1$, $\frac{1}{4} < c < \sqrt{2/\pi e}$, and sufficiently small c.

We have learned how the solutions would be related to c, but there is no closed-form solution so far. While the above results do provide valuable insight, they do not provide an adequate approximation to the solution. Applying the previously discussed numerical techniques, we explored the sequential trials for a large set of sampling cost parameter values. The numerical descriptions of the solutions are summarized in Figure 1 presenting the plots for the continuous time version for $c = 1.0$, 0.5, 0.25, and 0.1.

Given any fixed σ_0^2, σ^2, k, and c , we can calculate the optimal boundaries for the original discrete problem. First we implement the computer program with the standardized sampling cost $c^* = c\sigma^2 k^{-2}$, then apply (10) to adjust the optimal boundaries of the continuous time version problem. As an example, suppose $\sigma_0^2 = 5$, $\sigma^2 = 20$, $k = 1$, and $c = 0.001$, then

c^* equals 0.02, and the initial value s_0^* in the normalized scale is given by $s_0^* = k^{-1}s_0 = k^{-1}\sigma_0^2 = 5$. The dotted curve in Figure 2 is the optimal boundary of the continuous time problem in the normalized scale with sampling cost 0.02. Two hundred optimal boundary values of the original discrete problem are plotted and linked together with solid line segments within the continuation region of the continuous time problem. Some of the optimal outer and inner boundaries values, with notations y_n^{out} and y_n^{in}, are listed in Table 1. The optimal sequential rule for this example is to stop the trial at stage n if $|Y_n| \geq y_n^{out}$ or $|Y_n| \leq y_n^{in}$ and reject or claim bioequivalence, and continue the trial otherwise.

One alternative model is to consider that the cost of claiming bioequivalence is not μ^2, but $|\mu|$. This leads to a different stopping cost.

$$E[|\mu| \mid Y(s) = y] = s^{\frac{1}{2}}[G_1(\alpha) + G_1(-\alpha)], \tag{16}$$

where

$$\alpha = y\, s^{-\frac{1}{2}}\ , \ \ G_1(\alpha) = \varphi(\alpha) + \alpha\, \Phi(\alpha),$$

and φ and Φ are the density and cumulative distribution functions for the standard normal distribution.

Note that

$$G_1(\alpha) + G_1(-\alpha) = 2\ \{\varphi(\alpha) + \alpha[\Phi(\alpha) - \frac{1}{2}]\} = H_1(\alpha).$$

We have

$$d_2(y,s) = \frac{c}{s} + \ \min\ (0\ ,\ s^{\frac{1}{2}}H_1(\alpha) - 1\ ), \tag{17}$$

and we will call the sequential optimization problem related to d_2 problem 2, and the previous one problem 1. It is believed that the continuity regions of this problem should have shapes similar to those of problem 1. In particular when s is small both $d(y,s)$ and $d_2(y,s)$ are approximated by the same term c/s, representing the sampling cost, and so we expect similar behavior near $s = 0$.

The implementation of this second version is the same as of the previous one except for replacing the cost function $d(y,s)$ with $d_2(y,s)$. Figure 3 shows the shapes of the stopping boundaries are very similar for the two versions for four values of c.

7 Discussion

From the cost functions $d(y,s)$ and $d_2(y,s)$ defined in (6) and (17), we see the risk approaches infinity as $s \to 0$. In order to obtain better solutions for s near 0 , Bather and Chernoff (1988) suggest the following modification of $d(y,s)$ using asymptotic expansion technology. Let

$$J(\alpha) = e^{-\frac{1}{2}\alpha^2} \int_0^\alpha e^{\frac{1}{2}x^2}\, dx. \tag{18}$$

Note that $J'(\alpha) = 1 - \alpha\, J(\alpha)$ and both $s^{-\frac{1}{2}}J(\alpha)$ and $s^{-1}J'(\alpha)$ are solutions of the heat equation if $\alpha = y\, s^{-\frac{1}{2}}$. Hence, so is

$$cs^{-1}\{J'(\alpha_-) + J'(\alpha_+)\},$$

where

$$\alpha_- = \frac{y-1}{s^{\frac{1}{2}}} \text{ and } \alpha_+ = \frac{y+1}{s^{\frac{1}{2}}}.$$

Briefly, the modification consists of substracting a solution of the heat equation from d which does not change the optimal solution, but makes the derivation of asymptotic expansions for the solution easier by reducing the singularity due to the term c/s. By subtracting this solution from $d(y,s)$ in (6) and using $J'(\alpha) = 1 - \alpha J(\alpha)$, the new cost function d_1 is obtained :

$$d_1(y,s) = \min\{0, y^2 + s - 1\} + \frac{c}{s}\{\alpha_- J(\alpha_-) + \alpha_+ J(\alpha_+) - 1\}. \tag{19}$$

Note the solutions of this new cost function are the same as those of $d(y,s)$. Thus we may apply the numerical techique to $d_1(y,s)$ to compute the optimal boundaries near $(y,s) = (1,0)$. But it is very expensive to calculate the integral $J(\alpha)$ directly and to apply the numerical approximation using d_1. On the other hand asymptotic approximations to $J(\alpha)$ for small and large value of α can be used to provide asymptotic expansions for the boundary curves near the critical point $(y,s) = (\pm 1, 0)$. For small s; the boundary behaves like

$$\begin{aligned} \tilde{y_1} &= 1 - \frac{s}{2} - \frac{s^2}{8} + a_1 s^2 \\ \tilde{y_2} &= 1 - \frac{s}{2} - \frac{s^2}{8} + a_2 s^2, \end{aligned} \tag{20}$$

where $\tilde{y_1}$ applies to accepting bioequivalence, $\tilde{y_2}$ to rejection and there are symmetric curves near $y = -1$. The values of a_1 and a_2 are $a_1 = \frac{1}{6} - \frac{1}{2c}$ and $a_2 = \frac{1}{6} + \frac{1}{2c}$ respectively. Note that $1 - \frac{s}{2} - \frac{s^2}{8}$ describes the approximate behavior of the curve $y^2 + s = 1$ near $(y, s) = (1, 0)$.

For problem 2, Chernoff and Bather also suggest that there are almost symmetrical boundary curves near each critical point $(y, s) = (\pm 1,\ 0)$, at $y = 1 \pm O(s^2)$ and $y = -1 \pm O(s^2)$.

From the asymptotic result (20), we would expect to see the two boundaries close to each other for small values of s for large constant c. In order to demonstrate the numerical results for small values of s, we chose sufficiently small c values and computed the numerical approximations for $s < 1$. Figures 4 and 5 show clear pictures of the behavior of the boundaries near the critical points $(y, s) = (\pm 1, 0)$. We see, for problem 2, the estimated stopping boundaries are symmetric around $y = 1$. The angles of the curves get larger and the curves move forward as c becomes smaller. Note that a first set of numerical computations yielded the dotted curves in Figure 5 which did not agree well with asymptotic expansions for s close to zero. The continuous curves were calculated later, using a smaller initial step size and considerably more computer time. Even these more refined calculations can stand some improvement for s very close to zero, where asympototic expansions tend to be quite accurate.

We are also interested in how small c must be for the outer boundary curve to never return to $y = 0$. In general, we would like to see how the inner and outer curves behave as the sampling cost changes.

We have already learned from Bather and Chernoff (1988) that the inner curve and outer curve will meet at $(y, s) = (0, 1)$ for $c \geq 1$ for problem 1. As c decreases to 0, the inner critical s value, the s value where the inner curve reaches the s-axis, decreases to 0 and the outer critical s value increases to ∞ . Table 2 shows some of the estimated inner and outer critical values for problem 1. Note that Bather and Chernoff (1988) calculate a bound on the inner critical s value $s \geq 0.50$ for $c = 0.0554$ and the numerical result is $s = 0.5024$.

No bound was calculated for that value of c for which the outer curve never returns to $y = 0$. On the other hand, the numerical calculations indicate that when $c = 0.005715$, the outer curve is still moving away from $y = 0$ when s is 10^{31}. We also can get some insight from Figure 6. Similarly

for problem 2, the results are shown in Table 3 and Figure 7. When $c \geq 1$ the inner critical value and outer critical values meet at $s = 1.57$.

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Table 1

Estimates of stopping boundary of problem 1
sampling cost $c = 0.02$

stage	outer		inner	
n	s_n	y_n^{out}	s_n	y_n^{in}
0	5.0000000	6.100505		
1	4.0000000	5.539054		
2	3.3333333	5.085839		
3	2.8571429	4.718048		
4	2.5000000	4.414596		
5	2.2222222	4.167034		
6	2.0000000	3.944112		
7	1.8181818	3.760117		
8	1.6666667	3.596463		
9	1.5384615	3.446304		
10	1.4285713	3.3169861		
20	0.8333333	2.5330751		
30	0.5882353	2.1318240		
40	0.4545455	1.8871000		
50	0.3703704	1.7218550		
60	0.3125000	1.6052600	0.3125000	0.1656780
70	0.2702703	1.5146050	0.2702703	0.2799693
80	0.2380952	1.4439480	0.2380952	0.3691222
90	0.2127660	1.3873000	0.2127660	0.4412256
100	0.1923077	1.3404170	0.1923077	0.5001997
110	0.1754386	1.3018960	0.1754386	0.5499748
120	0.1612903	1.2694870	0.1612903	0.5918276
130	0.1492537	1.2416210	0.1492537	0.6281131
140	0.1388889	1.2176189	0.1388889	0.6593656
150	0.1298701	1.1968200	0.1298701	0.6866206
160	0.1219512	1.1788880	0.1219512	0.7101631
170	0.1149425	1.1629310	0.1149425	0.7314749
180	0.1086957	1.1490070	0.1086957	0.7504526
190	0.1030928	1.1365730	0.1030928	0.7674252
195	0.1005025	1.1308140	0.1005025	0.7752527

Table 2

Estimates of inner and outer critical values for bioequivalence problem 1

c	s – inner	s – outer
1.00	1.0000	1.0000
0.75	0.9997	1.0000
0.65	0.9872	1.0011
0.50	0.8973	1.0164
0.35	0.8667	1.0874
0.25	0.7891	1.2515
0.15	0.6778	2.0060
0.10	0.5999	4.7848
0.075	0.5508	20.059
0.065	0.5278	106.17
0.060	0.5169	1063.9
0.058	0.5102	19326.5
0.0575	0.5083	172112.6
0.05725	0.5082	4127510.8
0.0572	0.5062	26454535.0
0.05716	0.5062	8290124500.0
0.05715	0.5062	$>$ 2.11671245 (31)
0.0554	0.5024	
0.0500	0.4878	
0.0400	0.4561	
0.0300	0.4210	
0.0200	0.3730	
0.0100	0.3050	
0.0050	0.2549	
0.0010	0.1728	
0.0005	0.1487	
0.0001	0.1097	
0.00005	0.0977	
0.00001	0.0767	

Table 3

Estimates of inner and outer critical values for bioequivalence problem 2

c	s – inner	s – outer
1.00	1.5707	1.5707
0.75	1.5707	1.5708
0.50	1.5467	1.5738
0.35	1.4246	1.6304
0.25	1.2841	1.8043
0.10	0.9249	5.5226
0.06	0.7669	115.62
0.059	0.7637	153.05
0.056	0.7491	512.05
0.054	0.7393	2354.9
0.053	0.7339	10442.4
0.0525	0.7319	41255.5
0.0523	0.7301	100130.5
0.0521	0.7299	413058.6
0.052	0.7276	1401723.5
0.0519	0.7280	18049758.0
0.0518	0.7281	> 2.11671245 (31)
0.050	0.7191	
0.010	0.4150	
0.005	0.3397	
0.001	0.2321	
0.0005	0.2047	
0.0001	0.1585	

Figure 1 Boundary of bioequivalence problem 1

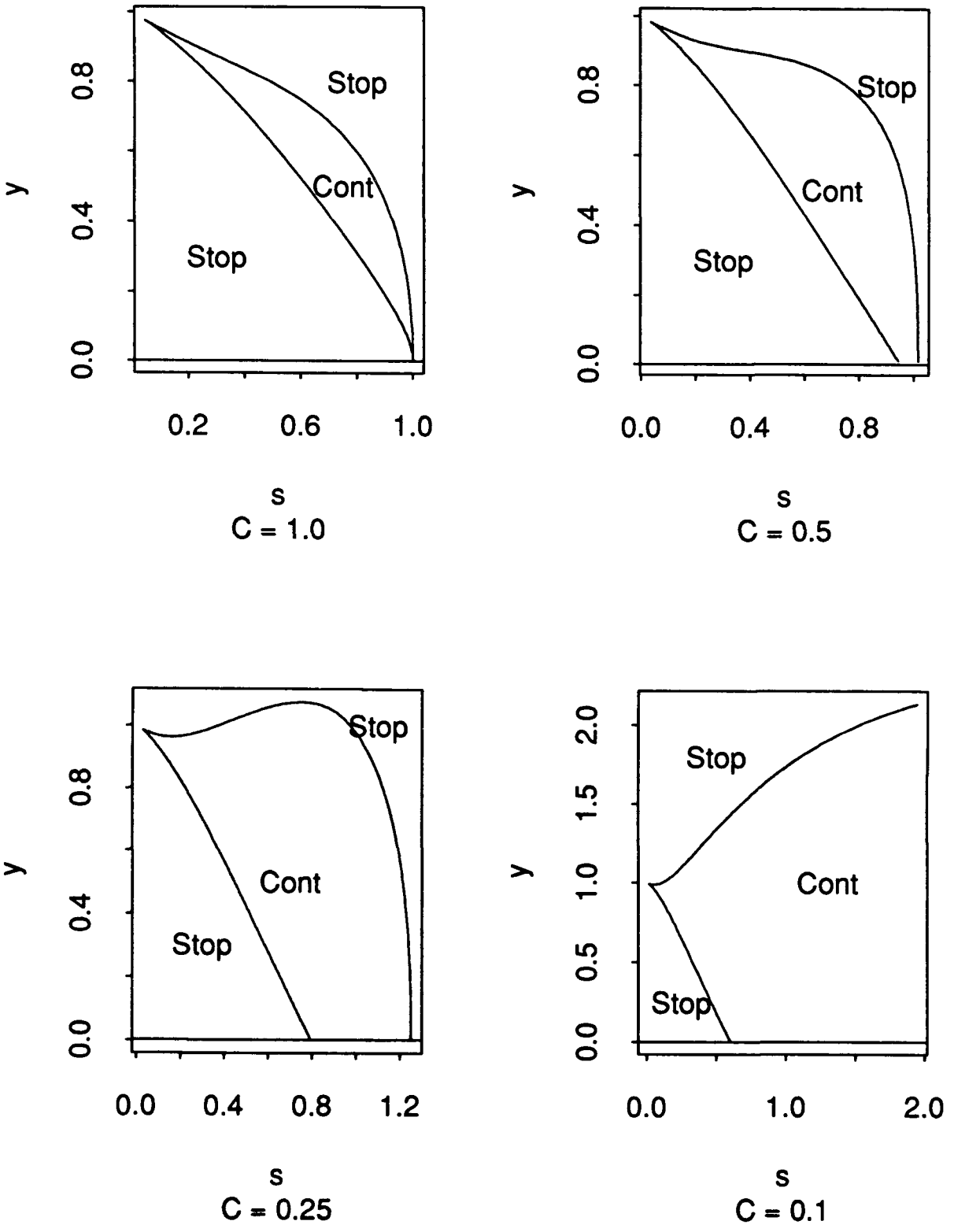


Figure 2 Boundary of original discrete problem 1

C=0.02

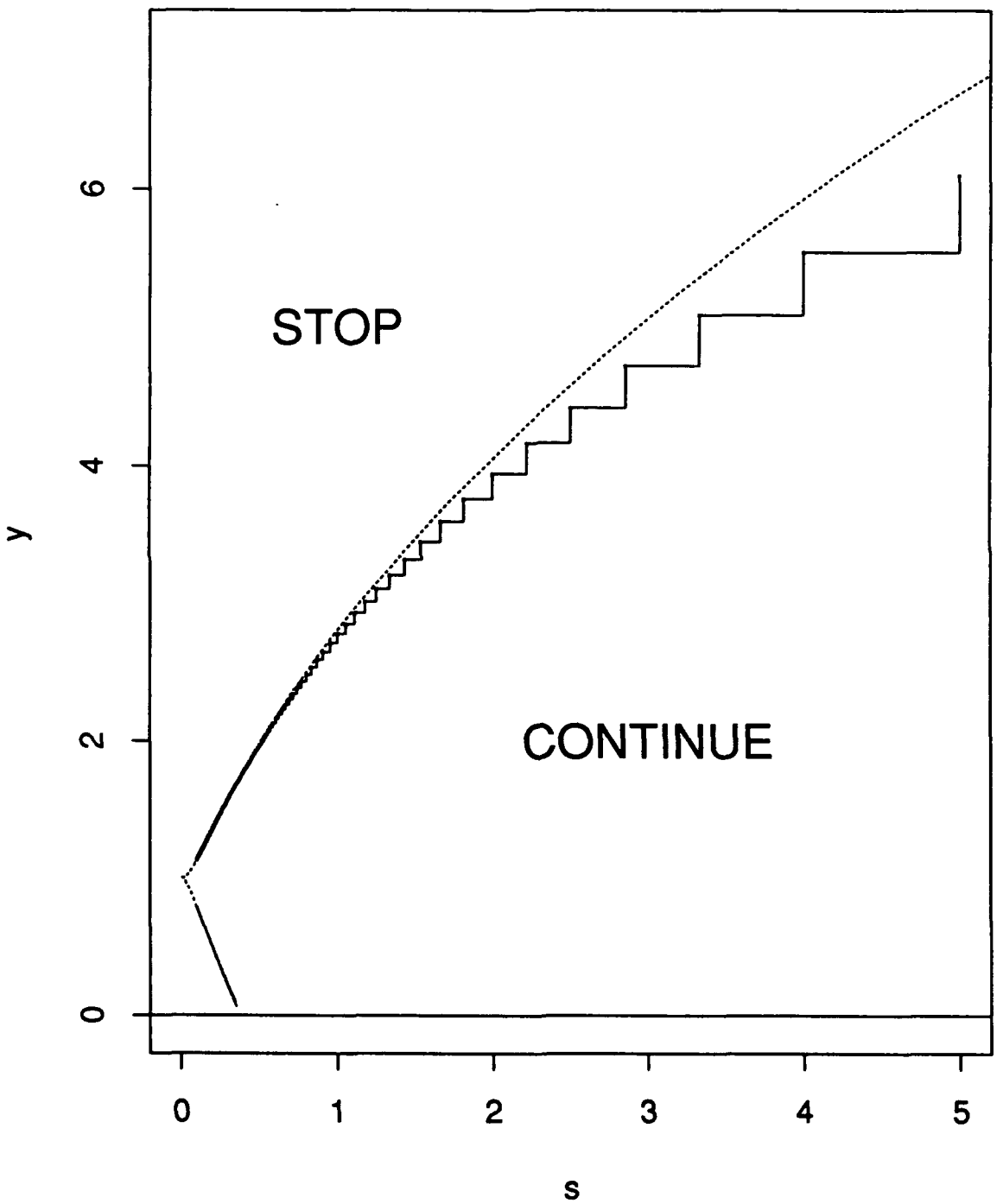


Figure 3 Boundary of bioequivalence problem 2

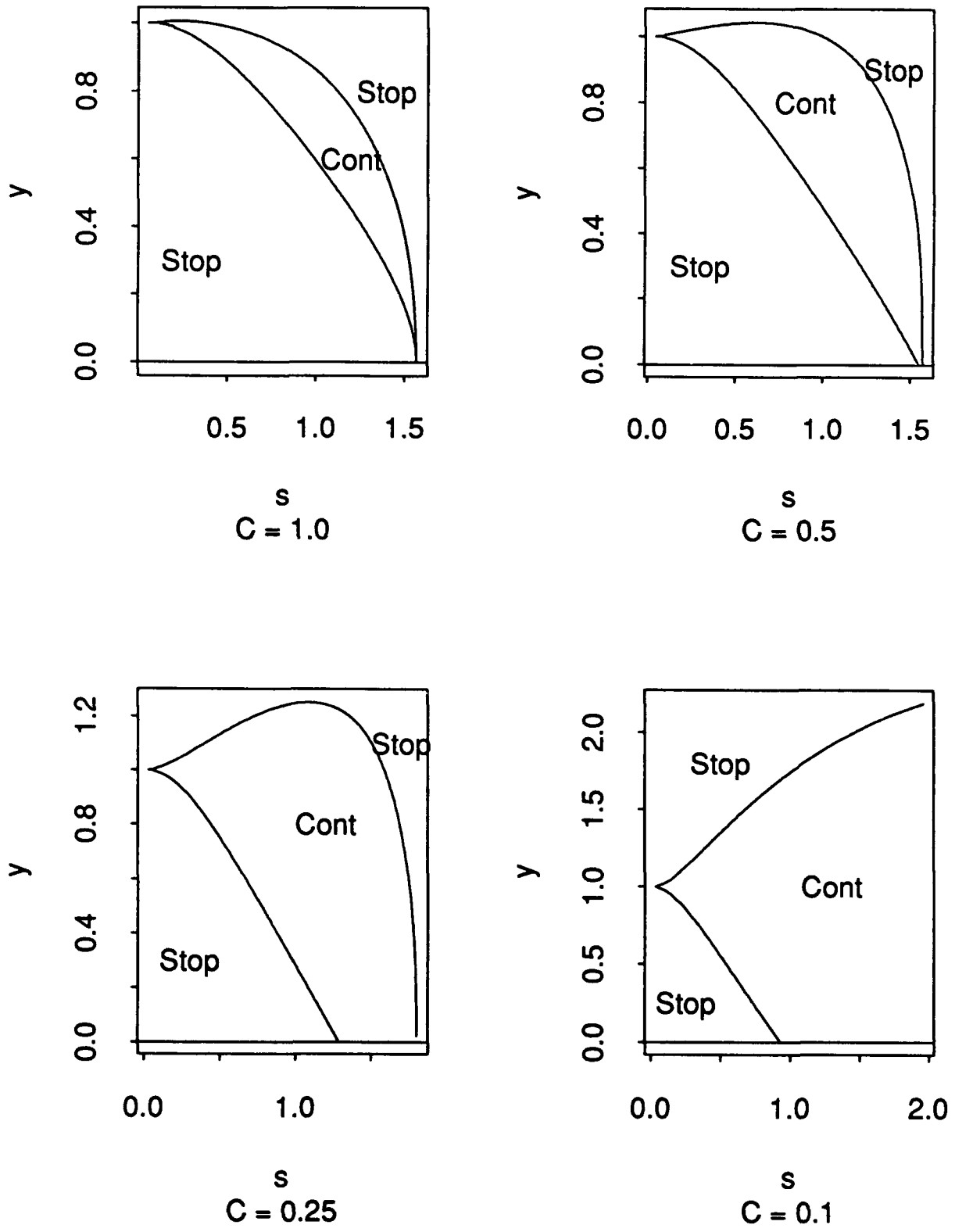


Figure 4 Stopping boundary of problem 1 -- small c

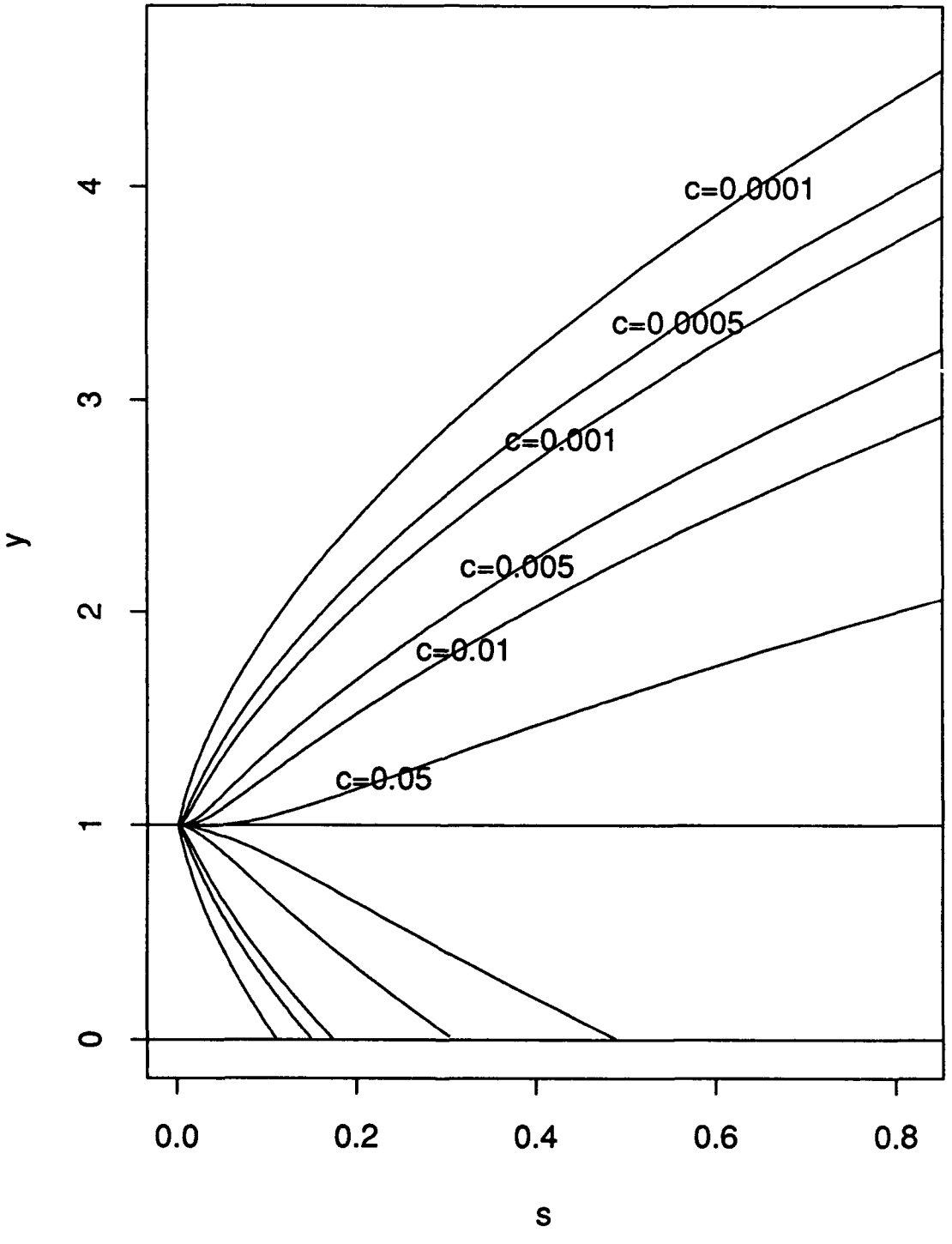


Figure 5 Stopping boundary of problem 2 -- small c

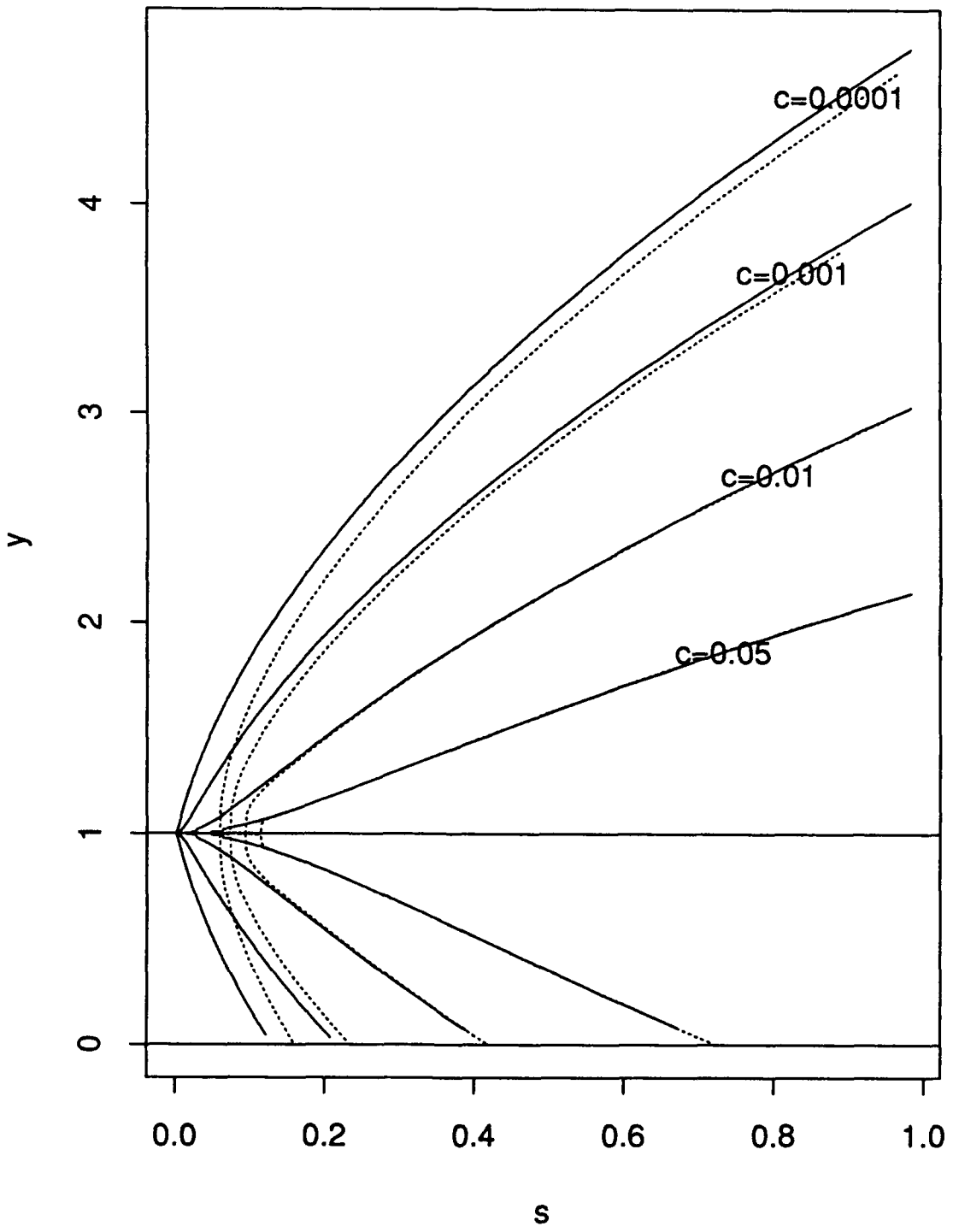
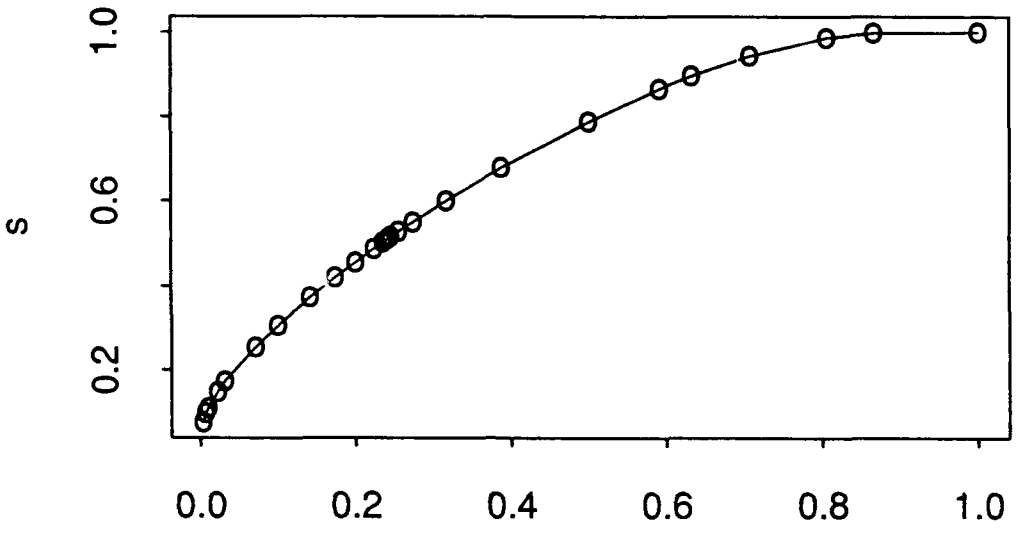
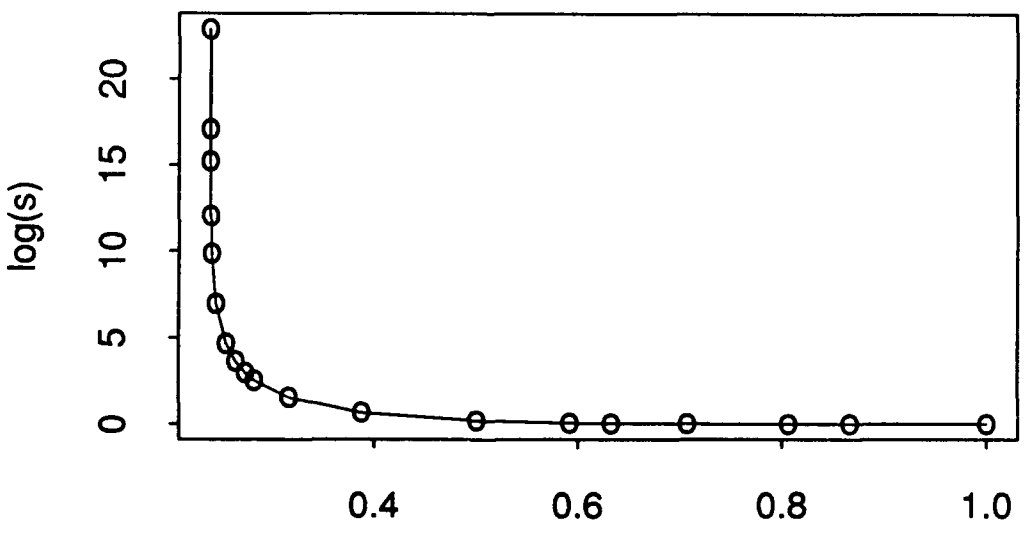


Figure 6 Inner and outer critical curve of problem 1

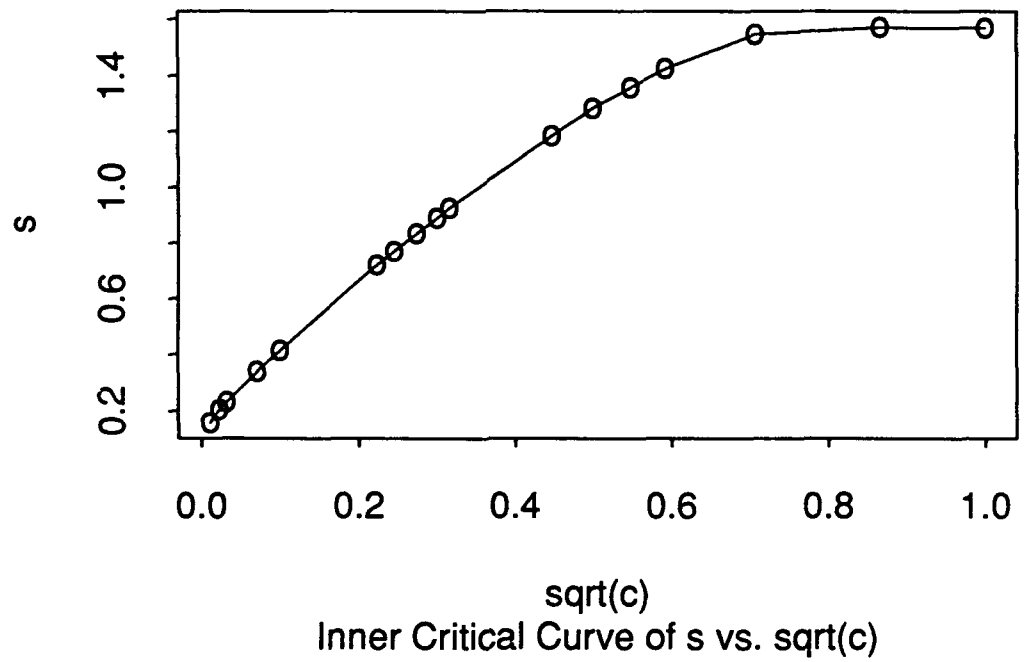


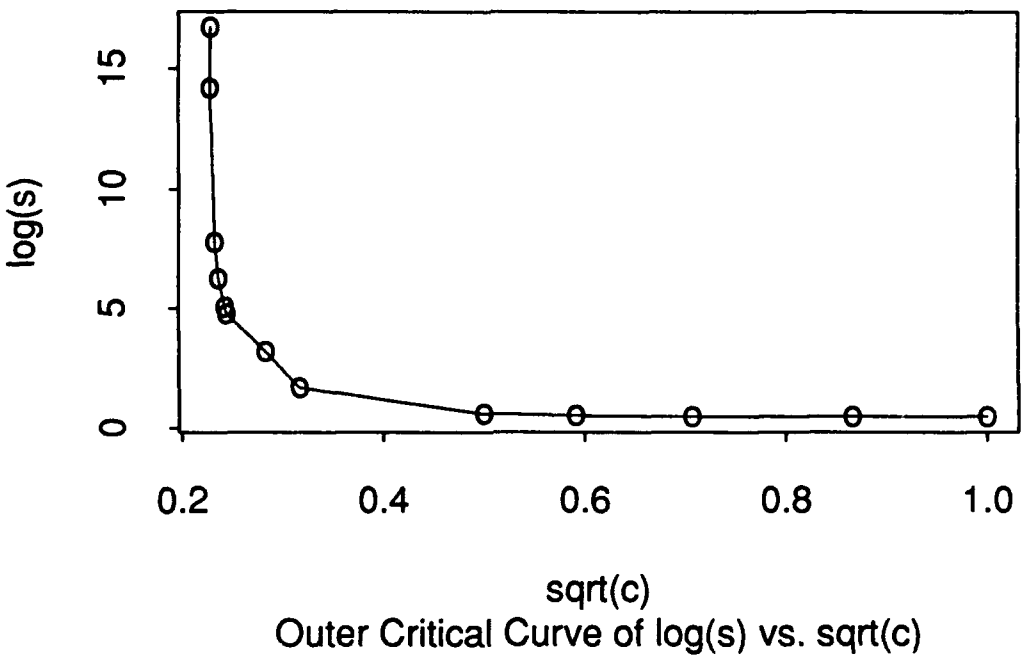
Inner Critical Curve of s vs. sqrt(c)



Outer Critical Curve of log(s) vs. sqrt(c)

Figure 7 Inner and outer critical curve of problem 2





ABSTRACT

Bioequivalence is an important area of pharmaceutical research containing many questions which are not yet resolved. Various statistical approaches have been discussed in the literatures. We address stopping rules for testing bioequivalence from a decision-theoretic point of view. The numerical techniques for Bayes sequential decision problem are employed to obtain explicit descriptions of the solutions of the continuous time optimal stopping problem on bioequivalence.

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